

## Effect of remedies for enhancing resistance and relieving blood stasis on metastasis in postoperative gastric cancer and ornithine decarboxylase levels

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### Abstract

**AIM:** To study the action of remedies for enhancing resistance and relieving blood stasis on metastasis in postoperative gastric cancer and its influence on ornithine decarboxylase (ODC).

**METHODS:** Sixty-three postoperative patients with gastric cancer were randomly divided into two groups. Thirty-one patients were treated with western medicine consisting of the FAP (5-fluorouracil, adriamycin, cisplatin) and CODP regimens (cyclophosphamide, vincristine, daunorubicin, prednisone), whereas 32 patients were treated with the FAP regimen and traditional Chinese medicine. Correlations were made between the ODC levels detected before and after treatment and other factors such as tumor diameter, infiltration depth, histological type, and lymph node metastasis.

**RESULTS:** The ODC levels in the gastric cancer tissue and adjacent normal gastric mucosal tissue were significantly higher in the patients than in the controls. There was an obvious correlation between increased ODC and tumor size, infiltration depth, degree of differentiation, and lymph node metastasis. Six months later, there were no significant changes in the ODC levels of the group using only Western medicine, while the ODC levels decreased markedly in the group using combined Western and traditional Chinese medicine ( $P < 0.01$ ).

**CONCLUSION:** The effects of traditional Chinese medicine remedies on metastases in postoperative gastric cancer are related to the reduction of ODC activity.

**Key words:** Stomach neoplasms/surgery; Neoplasms metastasis; Ornithine decarboxylase; Traditional Chinese medicine

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### INTRODUCTION

Ornithine decarboxylase (ODC) is the rate-limiting enzyme of polyamine synthesis in cellular proliferation. It has been proven that ODC mutagenesis and carcinogenesis play an important role in gastric cancer development, metastasis, and relapse. During the period of 1992-1994, the author studied the action of traditional Chinese medicine remedies for enhancing resistance and relieving blood stasis on metastases in postoperative gastric cancer and their effect on ODC levels at the Department of Medicine of Tokyo University, Japan.

### MATERIALS AND METHODS

Sixty-three postoperative patients with gastric cancer from the Department of Medicine, the Affiliated Hospital of Tokyo University, Japan, comprising 41 men and 22 women with a mean age of 63.2 years, were studied. Twenty-three cases of early gastric cancer and 40 cases of advanced gastric cancer were diagnosed histopathologically. Forty-two patients had differentiated carcinoma, including papillary and tubular adenocarcinoma (nine were grade I, eight were grade II, 25 were grade III-IV). Twenty-one patients had undifferentiated carcinoma, including six with undifferentiated adenocarcinoma, six with undifferentiated mucinous adenocarcinoma, four with poorly differentiated adenocarcinoma, and five with signet ring cell carcinoma. Thirty-nine patients had lymph node metastasis and 24 patients did not.

The 63 postoperative patients were randomly assigned to two groups. There were no significant differences ( $P > 0.05$ ) between the groups in terms of age, sex, general condition, surgical approach, tumor size, invasion depth, histological type, and metastasis. Thirty-one patients were treated with Western medicine involv-

Table 1 Mean ornithine decarboxylase levels in normal gastric mucosa before and after treatment (CO<sub>2</sub> nmol·mg protein<sup>-1</sup>·h<sup>-1</sup>)

	<i>n</i>	Pre-treatment	Post-treatment	Pre-treatment minus post-treatment ( $\bar{x} \pm s$ )
Traditional and Western medicine	32	246.9	191.7	55.1 ± 6.49
Western medicine only	31	239.9	225.1	14.8 ± 2.01

Table 2 Analysis of ornithine decarboxylase levels changes in normal gastric mucosa and related factors in study groups before and after treatment ( $\bar{x} \pm s$ )

		Traditional Chinese medicine and Western medicine		Western medicine only	
		Before	After ( <i>n</i> )	Before	After ( <i>n</i> )
Tumor diameter (cm)	< 4.9	194.2/128.4	65.7 ± 9.03 (18) <sup>a</sup>	188.3/181.8	6.5 ± 1.23 (16)
	≥ 5.0	26908/248.8	21.1 ± 4.63 (14)	270.1/262.1	8.0 ± 1.73 (15)
Histological type	Advanced cancer	288.3/261.8	26.5 ± 4.2 (20)	269.8/255.1	14.7 ± 2.95 (20)
	Differentiated	201.1/125.8	75.3 ± 10.89 (21) <sup>a</sup>	211.3/193.4	17.9 ± 2.27 (2)
Lymph node metastasis	Undifferentiated	288.5/268.8	19.7 ± 3.58 (11)	276.8/282.5	-5.7 ± 1.29 (10)
	Negative	198.8/176.5	22.3 ± 3.98 (13)	201.1/188.5	12.6 ± 3.13 (11)
	Positive	381.3/255.3	126 ± 17.17 (19) <sup>b</sup>	273.8/365.4	8.4 ± 1.09 (20)

Comparison before and after treatment, <sup>a</sup>*P* < 0.05, <sup>b</sup>*P* < 0.01.

ing the FAP regimen (5-fluorouracil, 300 mg/m<sup>2</sup> intravenous gutta for five consecutive days; adriamycin, 40 mg/m<sup>2</sup> for the first day), or the CODP regimens (cyclophosphamide, vincristine, daunorubicin, prednisone) (60 mg/m<sup>2</sup> intravenous gutta). Thirty-two patients were treated with the FAP regimen and traditional Chinese medicine. The powder of eight Noble Ingredients (ginseng, white atractylodes rhizome, Poria, *Pinellia*, 4 g each; tangerine peel and Fructus Ziziphi Jujubae, 2 g each; liquorice, 1 g; dried ginger, 0.5 g) was administered in 1-g doses three times per day. Pills of cinnamon twig and Poria (cinnamon twig, Poria, Moutan bark, peach seed, peony root, 4 g each) were administered in 3 g doses three times per day for 6 mo as one course of treatment. ODC levels were detected in specimens from the border between normal gastric mucosa tissues and tumor tissues using the Furihata method<sup>[1-3]</sup>.

In the two treatment groups, normal gastric mucosa near the anastomosis was biopsied and examined endoscopically in patients with no relapse 6 mo after surgery (10 patients without gastric cancer served as the normal control). The specimens were frozen in liquid nitrogen immediately and stored at -80 °C for ODC detection within 2 wk. The correlation was analyzed between each specimen, where the mean ODC value was detected twice.

## RESULTS

There were significant differences in the rate of relapse between the Western medicine group (three relapses) and Western medicine plus traditional Chinese medicine group (one relapse) within 6 mo. The ODC levels (CO<sub>2</sub> nmol·mg protein<sup>-1</sup>·h<sup>-1</sup>) of the normal controls was 83.2 ± 6.9 ( $\bar{x} \pm s$ ). The mean diameter of gastric cancer was 4.98 cm. The ODC levels in tumors with diameter < 4.9 cm and > 5.0 cm were 364.2 ± 47.3 and 598.8 ± 79.4, respectively. The ODC levels of early and advanced cancer, differentiated and undifferentiated tumors, and negative and positive lymph node metastases were 378.3 ± 49.5 and 563.4 ± 69.8, 441.3 ± 36.9 and 538.1 ± 77.3, and 358.5 ± 50.5 and 698.8 ± 151.2, respectively. There were no significant pre-treatment differences between the normal control (*P* > 0.05) and Western medicine groups (*P* > 0.05). Significant differences were found pre- and post-treatment in the Western medicine plus traditional Chinese medicine group (*P* < 0.01) (Table 1). There were no significant differences between the pre- and post-treatment gastric mucosa ODC levels in the Western medicine group. Significant post-treatment differences were found between the Western medicine group and the Western medicine plus traditional Chinese medicine group. The ODC changes in the normal gastric mucosa and related factors in the two groups before and after treatment are shown in Table 2.

Table 2 shows a significant correlation between the ODC levels of normal gastric mucosa and tumor diameter, infiltration depth, histological differentiation type, and lymph node metastasis. In the group using traditional Chinese medicine and Western medicine, the ODC

level was decreased in tumors with diameter < 4.9 cm, early gastric cancer, moderate differentiation, and positive lymph node metastases. The results suggest that traditional Chinese medicine remedies for enhancing resistance and relieving blood stasis against metastases in postoperative gastric cancer are correlated with reduced ODC activity.

## DISCUSSION

It has been proven that a close relationship exists between gastric cancer and the important mechanism of blood stasis at each stage of cancer formation. Our study showed that blood stasis in postoperative gastric cancer is similar to the high blood coagulation state in modern medicine (a condition where free cancer cells embed in the small blood vessels and infiltrate other tissues to form metastases foci). While these patients manifested blood stasis to a certain degree, their resistance was reduced because of the surgical damage. We used the powder of eight Noble Ingredients and cinnamon twig and Poria pills to treat the patients and tonify their *qi* (vital energy) and blood, promote blood circulation and remove blood stasis, and to strengthen body resistance to disease. Six months later, metastatic relapse was reduced and the ODC levels of the gastric mucosa were sharply reduced.

The results showed that the earliest biochemical reaction of human cells treated with carcinogenic agents is rapid and that there is significant induction of ODC activity. Acting with early mutagens, ODC obviously promotes metastases and malignancy. The ODC levels in the gastric cancer tissue and the adjacent normal gastric mucosa tissue in our patients were significantly higher than that in the controls. The extent of ODC increase was obviously correlated with tumor size, infiltration depth, degree of differentiation, and lymph node metastases. Six months later, the ODC levels were not significantly different in the group treated with only Western medicine, while there was a significant decrease of ODC levels in the group using Western medicine and traditional Chinese medicine. This suggests that the effect of traditional Chinese medicine against metastases in postoperative gastric cancer is related to the reduced ODC levels. However, how the anti-metastasis effect of traditional Chinese medicine in postoperative gastric cancer is yielded by reducing ODC activity awaits further studies.

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